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HOMOZYGOSITY MAPPING IN 4 UNRELATED IRANIAN FAMILIES WITH AUTOSOMAL RECESSIVE MENTAL RETARDATION IDENTIFIES OVERLAPPING LINKAGE INTERVALS ON CHROMOSOME REGION 1p34: A FREQUENT CAUSE OF ARMР?

Hossein Najmabadi^{1,3}, Masoud Garshasbi², Ideh Bahman¹, Shirin Ghadami¹, Mohammad Mahdi Motazacker², Lia Abbasi-Moheb², Sahar Esmaeeli Nieh², Lucia Puettmann², Klaus Wrogemann², Farkhondeh Behjati¹, Roxana Kariminejad³, Marzieh Mohseni¹, Mohhamad Javad Soltani Banavandi¹, Hossein Dravish¹, Peiman Jamali⁴, Yasser Heshmati¹, Poneh Nikoui⁵, Farin Soleimani¹, Hao Hu², Chen Wei², Kimia Kahrizi¹, Andreas Tzschach², Andreas Walter Kuss², Hans Hilger Ropers²

University of Social Welfare and Rehabilitation Sciences, Tehran, Iran¹

Max-Planck-Institute for Molecular Genetics, Berlin, Germany²

Kariminejad-Najmabadi Pathology and Genetics Center, Tehran, Iran³

Shahroud Welfare Institution, Shahroud, Iran⁴

Bandar Abbas Welfare Institution, Bandar Abbas, Iran⁵

Compared to X-linked mental retardation, autosomal recessive MR has received very little attention so far, and in particular, this holds for non-syndromic forms (NS-ARMR). To date, only 13 loci for NS-ARMR and no more than 5 genes for this condition have been published. Recently, homozygosity mapping in 78 families with NS-ARMR has revealed that this condition is extremely heterogeneous (Najmabadi et al, 2007). Indeed, two recurrent mutations have only been observed in a single gene (Garshasbi et al, 2008; Molinari et al, 2008), suggesting that there are no frequent genetic causes of NS-ARMR. However, in the course of an ongoing large-scale investigation into the molecular causes of ARMР, we have now identified four consanguineous families, three with non-syndromic and one with syndromic ARMР, all with a single homozygous interval on chromosome 1p34. This is the most conspicuous clustering of linkage intervals observed in our entire cohort, which comprises a total of >250 consanguineous Iranian families that have undergone homozygosity mapping so far. Therefore, it is tempting to speculate that the underlying defect in three or even all four of these families involves the same gene locus, MRT4, which may well account for several percent of the mutations causing ARMР in the Iranian population. The region of overlap between these intervals comprises 7.7 Mb, and it encompasses 128 genes. Mutations in the coding regions of two candidate genes for syndromic forms of MR, *STIL* and *POMGNT1*, were excluded by Sanger sequencing. Chromosome sorting and next generation sequencing, a novel strategy recently pioneered in our laboratories, is now in progress to speed up the search for the underlying gene defect or defects. Results of these studies will be reported.